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(71) Applicant *(for all designated States except US)*: ROBERTET S.A. [FR/FR]; 37, av. Sidi Brahim, F-06330 Grasse (FR).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)* : BETTS, John, Adrian [GB/GB]; Valhalla, New Road, Haslemere, Surrey GU27 3RW (GB).

(74) Agent: GEE & CO.; Chancery House, Chancery Lane, London WC2A 1QU (GB).

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(54) Title: INHIBITORS OF ESTERASE-PRODUCING MICRO-ORGANISMS, FOR USE PRIMARILY IN DERMATOLOGY AND COSMETICS

(57) Abstract

Inhibitors of esterase-producing micro-organisms, primarily for use in dermatology and cosmetics and with particular application to personal deodorants and to anti-fungal agents and other preparations for the treatment of acne, dandruff and tinea pedis. The active ingredient of the inhibitor comprises an aromatic acid ester of a phenol or of an aromatic alcohol, the phenol or aromatic alcohol being sufficiently water-soluble to impart an anti-microbial action and the aromatic acid being sufficiently water-soluble to impart an anti-microbial action and/or to lower the pH of liquid body-secretions to a level which at least inhibits the growth of micro-organisms in the liquid body-secretions.

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INHIBITORS OF ESTERASE-PRODUCING MICRO-ORGANISMS, FOR USE PRIMARILY IN DERMATOLOGY AND COSMETICS

This invention relates to inhibitors of esterase-producing micro-organisms. The inhibitors are for use primarily in dermatology and cosmetics and have particular application to personal deodorants and to anti-fungal agents and other preparations for the treatment of acne, dandruff and tinea pedis.

The human skin has a large natural population of micro-organisms. These organisms are nourished by various skin secreted substances, skin cell debris, breakdown products of the skin and the organisms themselves. The skin secretions are conveniently divided into two groups, water- and lipid-soluble materials; these are eccrine and apocrine sweat and sebum which will be referred to as 'liquid body-secretions' and will now be described, as will their functions as are generally understood.

Eccrine sweat consists mainly of a watery solution of dissolved salts and is produced by glands distributed over the whole skin surface. In conditions of occlusion, e.g. feet enclosed in socks and shoes, the eccrine sweat accumulates and in these warm, damp conditions, the skin debris, together with nutrients from the sweat, provide a medium for micro-organism growth with the possibility of massive overgrowth of one type. This can result, in the first instance, of odorous metabolic products, and in the second, of clinical infection with maceration of the skin and irritation.

Apocrine sweat is produced by the apocrine glands at specific sites on the body, notably the axillae,

the anogenital area and around the nipples. Although present at birth, the apocrine glands are not functional until puberty when they are influenced by circulating androgens. Apocrine secretion differs from eccrine sweat in containing lipids (fatty materials) and proteins. In the warm, damp occlusion met in the axilla, certain skin micro-organism metabolise this secretion, forming free fatty acids and other breakdown products. These materials are odorous and responsible for 'body odour'.

The sebaceous glands are distributed over the skin surface except the palms and dorsae. They are most numerous on the scalp, forehead, face, back and chest. The secretion, sebum, consists mainly of fatty materials, wax esters, cholesterol and its esters and squalene. Normally, sebum flows freely from the glands, spreading over the skin surface. In acneic and certain other skin conditions, the sebaceous duct through which the sebum is normally secreted becomes hyperkeratinised and the opening of the duct becomes blocked. The gland continues to produce sebum and the blocked duct distends to form a comedone. Also blocked in the duct, (the normally) commensal micro-organisms produce esterases which hydrolyse the sebum lipids, liberating free fatty acids. These fatty acids are irritant and can result in an inflammatory reaction along the wall of the duct. Leucocytes invade the inflamed area and the comedone develops into papule and then a pustule. This is a typical acne 'spot'.

The scalp is well supplied with sebaceous glands, and the scalp, like all skin, undergoes desquamation. Due to the presence of hair, the squames tend to be retained at the scalp surface. Sebum accumulates beneath these squames and in dandruff conditions is hydrolysed

by micro-organism produced esterases to form irritant fatty acids. The irritation causes proliferation of the epidermis and increased formation of the stratum corneum which again desquamates unevenly in large clumps - the dandruff scale or flake.

It is an object of the present invention to provide effective inhibitors of esterase-producing micro-organisms, and also preparations incorporating such inhibitors for use in dermatology and cosmetics; one specific object to to provide a personal deodorant having a formulation which produces effective action over a substantial period of time, which is safe in application, and which is economical and safe to produce.

According to a principal aspect of the present invention, there is provided an inhibitor of esterase-producing micro-organisms, in which the active ingredient comprises an aromatic acid ester of a phenol or of an aromatic alcohol, the phenol or aromatic alcohol being sufficiently water-soluble to impart an anti-microbial action and the aromatic acid being sufficiently water-soluble to impart an anti-microbial action and/or to lower the pH of liquid body-secretions (as hereinbefore referred to) to a level which at least inhibits the growth of micro-organisms in the body-secretions.

For use in deodorants, the active ingredient can be incorporated in a suitable perfume composition which is then incorporated in a vehicle such as ethanol; for use in a dermatological composition, the active ingredient can be incorporated in an acceptable vehicle containing for example, a polyol or dimethyl sulphoxide which may also act as a skin penetrant.

The effect of the active ingredient is produced

by the aforementioned microbial enzymes acting to split the constituents of the ester and so hydrolyse the ester back into the aromatic acid and the phenol or aromatic alcohol. On a skin surface, such as in deodorant applications, this action occurs almost immediately but where skin penetration is involved, as in most dermatological applications, the action is progressive.

The above term 'anti-microbial action' means an action which inhibits microbial growth, rather than one which eliminates microbial growth completely as can be achieved by a microbicide. In such skin-surface and skin-penetrating applications, the esterases produced by the micro-organism hydrolyse a portion of the active ingredient and, in so doing, inhibit the action of the esterase and further growth of the micro-organism. After a period of time, the micro-organism may resume its metabolic activity and the above-described process is repeated, and repetition will occur until the active ingredient is used up.

'Phenols' are, generally, aromatic compounds containing one or more hydroxyl groups directly attached to a benzene nucleus, but the phenols of the present invention may be restricted to those in which the other positions available on the benzene nucleus are more or less occupied by hydrogen, hydroxyl, aliphatic, benzenoid or heterocyclic groups. Examples of such phenols useful in the present invention include phenol, cresols, xylenols, thymol, carvacrol, eugenol and isoeugenol.

'Aromatic alcohols' are, generally, aromatic compounds with a hydroxyl group in a side chain attached to a benzene nucleus. Again, for the present invention, it is preferable that the other positions available on the benzene nucleus are more or occupied by hydrogen,

hydroxyl, aliphatic, benzenoid or heterocyclic groups. Suitable examples include benzyl alcohol, phenylethyl alcohol, cinnamic alcohol and anisic alcohol.

'Aromatic acids' are, generally, compounds containing one or more carboxylic groups which are directly attached to a benzene nucleus or occur in a side chain. Yet again, it is preferable that the other positions available on the benzene nucleus are occupied by hydrogen hydroxyl, aliphatic, benzenoid or heterocyclic groups. Suitable examples include benzoic acid, salicylic acid, cinnamic acid, phenyl-acetic and anisic acid.

The inhibitor according to the invention incorporates a microbial-inhibiting agent as opposed to the more usual triclosan bactericide which acts to eliminates rather than control the relevant microflora. Known microbicides and bactericides are usually powerful, and it is believed that the complete elimination of microflora, specifically cutaneous flora, is medically undesirable.

Embodiments of the present invention will now be described, by way of example.

As a deodorant for use in an aerosol spray or mechanical spray container, about 5% to 50% and preferably 20% of active ingredient of the invention is incorporated in a perfume composition, and about 1% of the perfume composition is added to a 96% ethanol excipient. The perfume composition of the invention will frequently be sold to an end-producer who will add the composition to his chosen vehicle.

As a dermatological agent in the form of a skin lotion, for the treatment of acne, between 0.5% and 20% and preferably about 5% of active ingredient

is incorporated in a vehicle which may be composed of dimethyl sulphoxide, polyol, ethanol and water in suitable proportions. Anti-inflammatory substances such as hydrocortisone or glycyrrhetic acid and healing agents such as allantoin, may also be incorporated in the end product.

As a scalp lotion for the treatment of dandruff, active ingredient within the above percentages is incorporated in a hydro-alcoholic vehicle, using solubilising agents as necessary.

As a powder for the treatment of tinea pedis and foot odour, active ingredient (if liquid), within the above percentages, is adsorbed onto amorphous silica powder or light magnesium carbonate which is then mixed with say 50% talcum, starch or other suitable powder. If the active ingredient is solid, usually crystalline, the crystals are finely ground, for example in a microniser, and then mixed with say 50% talcum, starch or other suitable powder.

Suitable perfume compositions may also be incorporated in the scalp/skin lotions and foot powders.

The skin and scalp lotions may be supplied in sprinkler bottles for application to the scalp or the affected skin area in the form of liquid droplets which are massaged into the scalp/skin. Alternatively, the lotion may be applied by means of a pad or compress which is pre-impregnated and supplied in a sealed package; the pad is partially exposed and then applied to an affected skin area, at least once per day. In further alternative forms, the inhibitors for use in treating the scalp or skin may comprise ointments, gels, creams, lotions, sprays or powders.

The inhibitors for foot treatment are preferably in powder form, as indicated above, but might also be supplied as liquids or in sprays etc.

CLAIMS

1. An inhibitor of esterase-producing micro-organisms, in which the active ingredient comprises an aromatic acid ester of a phenol or of an aromatic alcohol, the phenol or aromatic alcohol being sufficiently water-soluble to impart an anti-microbial action and the aromatic acid being sufficiently water-soluble to impart an anti-microbial action and/or to lower the pH of liquid body-secretion (as hereinbefore referred to) to a level which at least inhibits the growth of micro-organisms in the liquid body-secretions.

2. An inhibitor as claimed in Claim 1, wherein the available positions on the benzene nucleus of said phenol are more or less occupied by hydrogen, hydroxyl, aliphatic, benzenoid or heterocyclic groups.

3. An inhibitor as claimed in Claim 2, wherein said phenol is selected from phenol, cresols, xylenols, thymol, carvacrol, eugenol and isoeugenol.

4. An inhibitor as claimed in any preceding Claim, wherein the available positions on the benzene nucleus of the aromatic alcohol are more or less occupied by hydrogen, hydroxyl, aliphatic, benzenoid or heterocyclic groups.

5. An inhibitor as claimed in Claim 4, wherein said aromatic alcohol is selected from benzyl alcohol, phenylethyl alcohol, cinnamic alcohol and anisic alcohol.

6. An inhibitor according to any preceding Claim, wherein the positions available on the benzene nucleus of said aromatic acid are more or less occupied

by hydrogen, hydroxyl, aliphatic, benzenoid or heterocyclic groups.

7. An inhibitor as claimed in Claim 6, wherein said aromatic acid is selected from benzoic acid, salicylic acid, cinnamic acid, phenyl-acetic acid and anisic acid.

8. An inhibitor as claimed in any preceding Claim, wherein said active ingredient comprises phenol ester or aromatic alcohol ester.

9. An inhibitor as claimed in any preceding Claim, wherein said active ingredient is incorporated in a perfume composition which is then incorporated in a vehicle.

10. An inhibitor as claimed in Claim 9, wherein 5%-50% of said active ingredient is incorporated in said perfume composition and approximately 1% of the perfume composition is added to an approximately 96% ethanol excipient.

11. A deodorant having an inhibitor as claimed in any preceding Claim and wherein said active ingredient is incorporated in a vehicle which comprises an alcohol.

12. A dermatological agent having an inhibitor as claimed in any of Claims 1 to 8 and wherein said active ingredient is incorporated in a vehicle which comprises aqueous alcohol and/or skin penetrants.

13. A dermatological agent as claimed in Claim 12 and further incorporating anti-inflamatory substances and/or healing agents.

14. The use of an inhibitor as claimed in any of Claims 1 to 10, as a dermatological agent.

15. The use of an inhibitor as claimed in any of Claims 1 to 10, to produce agents against esterase-producing micro-organisms.

AMENDED CLAIMS

[received by the International Bureau on 29 October 1987 (29.1-.87); original claims 14 and 15 replaced by amended claims 14 and 15 (1 page)]

14. A compound which inhibits esterase producing micro-organisms, comprising an aromatic acid ester of a phenol or of an aromatic alcohol, the phenol or aromatic alcohol being sufficiently water-soluble to impart an anti-microbial action and the aromatic acid being sufficiently water-soluble to impart an anti-microbial action and/or to lower the pH of liquid body-secretion (as hereinbefore referred to) to a level which at least inhibits the growth of micro-organisms in the liquid body-secretions, the compound being for use in the preparation of a medicament to provide a deodorant effect.

15. A composition for topical application to the skin and which inhibits esterase producing micro-organisms to provide a deodorant effect, comprising:

(a) an effective amount of an aromatic acid ester of a phenol or of an aromatic alcohol, the phenol or aromatic alcohol being sufficiently water-soluble to impart an anti-microbial action and the aromatic acid being sufficiently water-soluble to impart an anti-microbial action and/or to lower the pH of liquid body-secretion (as hereinbefore referred to) to a level which at least inhibits the growth of micro-organisms in the liquid body-secretions; and,

(b) a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 87/00323

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 7/32; A 61 K 31/235

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0039857 (HENKEL) 18 November 1981 see claims; page 1, line 1 - page 2, line 16; page 2, line 25 - page 3, line 19; examples	1,6,7,9-15
X	US, A, 3808319 (KANFOUSH) 30 April 1974 see claims; column 1, lines 19-35	1-8,10,12, 14
X	BE, A, 458964 (GAZAN) 1 July 1945 see claims	1-9,12
X	DE, A, 2617817 (HENKEL) 10 November 1977 see claims; page 3, lines 19,24; page 5, lines 1-22; page 7, lines 3-5	1-10,12,13
X	FR, A, 2374039 (PROCTER & GAMBLE) 13 July 1978 see claims; page 1, line 1 - page 2, line 11; page 5, lines 11-24 and line 25 - page 2, line 2; page 16, example 1	1-10,12,14
X	FR, A, 2374292 (PROCTER & TAMBLE) ./.	

* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
6th August 1987	28 AUG 1987
International Searching Authority	**Signature of Authorized Officer**
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	13 July 1978 see claims; examples II,IV,V,X,XIV: "Solution"	1-10,12,14
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X	FR, A, 2390160 (HENKEL) 8 December 1978 see claims; page 2, lines 6-25; example 4	1-10,12,14
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X	EP, A, 0054174 (HENKEL) 23 June 1982 see claims; page 12, compound O	1-10,12,14

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 87/00323 (SA 17116)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 14/08/87

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0039857	18/11/81	DE-A-	3018114	19/11/81
US-A- 3808319	30/04/74	CA-A-	955852	08/10/74
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		JP-A-	57123109	31/07/82
		US-A-	4493823	15/01/85

INTERNATIONAL APPLICATION NO. PCT/GB 87/00323 (SA 17116)